International Journal of Food Science and Nutrition
ISSN: 2455-4898; Impact Factor: RJIF 5.14
Received: 01-10-2020; Accepted: 15-10-2020; Published: 03-11-2020
www.foodsciencejournal.com
Volume 5; Issue 6; 2020; Page No. 21-29

Micronutrients: Joining the dots for a holobiont nutrition

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Abstract

Holistic nutrition should consider the human being in its entirety as a holobiont, a complex mixture of various species of microbes and eukaryotic cells. Given this paradigm, only merging together the knowledge derived from state of the art science can allow us to integrate the needs of the holobiont with the data from nature . Accordingly, the decrease in micronutrient qualitative and quantitative composition in our soil force us to reconsider the need for supplementation as a means for obtaining the maximum benefit from foods: the supply of vital micronutrients (vitamins and minerals). Supplementation is now becoming a must. Reasons will be explained and solutions discussed. Certain fundamental vitamins and their daily amounts will be introduced briefly focusing on their support for the holobiont. Overall, the necessity to define practical quantities of micronutrients beyond those already specified by Health Authorities are briefly evaluated. Special importance is given to two key micronutrients which have peculiar properties of regulators of the delicate equilibrium within the holobiont: vitamin C and iodine. In conclusion, it is proposed that a safe and maximally beneficial range of micronutrients can be set at about 40 times the average daily allowance as identified by HA. The end-result is to allow the holobiont to regain the equilibrium sought by ancient medicine.

Keywords: Holistic, nutrition, holobiont, Micronutrients

1. Introduction

It has previously been discussed that nutrition should provide the macronutrients necessary for human life and health, avoiding particular foods that have a negative effect on immune system of the individual [1]. The use of special foods which are adapted to the individual based on their proper ABO blood typology has been explained with the recent advances in glycochemistry and glycobiology and the demonstration of the presence of glycans in foodstuff [2]. More recently, this concept of whole nutrition has been expanded with the paradigm shifting theory in biology dictated by the notion of the holobiont. As a holobiont, human beings are a true ecosystem of many diverse species of microbes (bacteria, fungi, protozoa, viruses, etc.) resident inside, within and on the body of human beings [3-5]. Within this frame of reference nutrition has been conceived as the prejudiced use of food to maintain the equilibrium between the varied species of microbes and the host.

Given this paradigm, only by merging together the knowledge derived from state of the art science as previously defined it will be possible to develop a holistic view of nutrition that can contemplate the human being as a holobiont. It will be maintained that this vision can further be extended to include the use of special nutrients to improve health for the whole holobiont [6]. These nutrients should be consumed by the holobiont in quantities sufficient for obtaining the maximum effect that is required. By keeping this in mind, it will be possible to merge together ancient knowledge that integrate the needs of the holobiont with modern science that has accumulated useful data from nature.

Vitamins and minerals, collectively referred to as micronutrients, are known to have important influences on everyone’s health, and their essential nature was recognized through the identification of clinical conditions and animal experiments [7] Micronutrients help the body use macronutrients, maintain health, develop optimal physiological functions and support many body processes [8]. Micronutrients are as important as macronutrients (carbohydrates, fatty acids and proteins) [1], so much so that their reduced consumption will inevitably lead to detrimental clinical consequences and even to increased risk of morbidity and mortality [9].

These clinical conditions, known as deficiencies, are commonly thought to be avoided by consuming an adequate daily intake of micronutrients from foods [10]. National and international guidelines and recommendations have been instituted by the Health Authorities (HA) of many Countries to tackle the issue of malnutrition (reduced consumption of essential micronutrients), including the World Health Organization (WHO) [11]. The European Food and Safety Agency (EFSA) has identified in a report of 2006 and other guidelines the minimum criteria for evaluating for minimum and maximum limits (thresholds) for micronutrients (EFSA, 2006). These thresholds have to take into consideration the following criteria:

1. no-observed adverse effect level (NOAEL), which is defined as the highest intake of a nutrient at which no adverse effects/events (AEs) have been observed;
2. lowest observed adverse effect level (LOAEL), being the lowest amount at which an AE has been demonstrated/observed. This value will normally be used if a NOAEL has not been established;
3. tolerable upper intake level (UL), which is result of the application of an uncertainty factor to the NOAEL or LOAEL. The UL represents a lower estimate of the threshold above which the risk of AEs may increase. The ULs can be seen as a safety range: within the UL a

daily intake is considered safe with no AEs

By defining these fundamental values, the EFSA has established the dietary reference values (DRV) for micronutrients (EFSA, 2019). DRVs are a complete set of reference values for nutrient consumption, something like adequate and reference ranges for micronutrients. At the same time, if not earlier, the US Food and Drug Administration (FDA) together with the National Institutes of Health (NIH) has also established the principles and guidelines of adequate dietary intake of micronutrients by defining the dietary reference intakes (DRI), which include ULs (NIH, 2019).

Hence, both the EU and the US have convened on the minimum doses of micronutrients necessary to be consumed by every human being to avoid the clinical manifestation of the deficiency condition. The setting of these limits occurred over several years through various experiments, including bioavailability considerations [12]. This minimum dose is often deemed to be the dose below which a deficiency is clinically evident. The NIH (Office of Dietary Supplements) have collaborated to set the average daily level of intake of nutrients which is sufficient to meet the requirements of nearly all a healthy population (NIH, 2019). These limits have been called recommended dietary allowance (RDA).

Although it may be debatable whether these amounts actually are sufficient for the minimum needs of each individual, the actual optimum amount may be further removed from these quantities. Indeed, there are situations where the amount needed for a healthy lifespan is likely to be much higher than the amount needed to prevent acute deficiency disease [13].

The fundamental realization that micronutrients interact with one another has led to the concept of full range supplementation (adequate overall nutrition) during each phase of life to avoid or reduce risk factors connected with micronutrient deficiency [14]. Foodstuff should not be considered just a way to satisfy our mere energy requirement but as a means for the provision of essential molecules that we cannot synthesize and that are essential for life.

There are many reasons why the amounts of micronutrients present in foods are not sufficient for our most basic needs as there are many reasons why these amounts are simply not present in foods anymore. But the most important is surely related to soil impoverishment.

Soil impoverishment

Soil impoverishment is the unwanted expected or unexpected removal of nutrients from the soil. Soil impoverishment is not to be confused with reverse fertilization, which is the voluntary man-made removal (principally nitrogen) used in forestry industry for the purpose of growth promotion of certain species over others [15].

Intensive agricultural practices can degrade the ecosystem, especially the soil which is the centre of a complex agrosystem (consisting of plant roots, the soil microflora, the soil fauna and the abiotic geochemical soil matrix) [16]. The degradative processes of intensive practices result in soil erosion and loss of available nutrients, organic matter and microbial propagules [17]. In general, soil degradation has a direct impact on the soil biosphere as it reduces the size of the microbial population [18], thereby indirectly affecting the homeostasis of the plants

Causes

It is well known that the introduction of herbivores in a territory (intensive cattle production) can affect directly and indirectly the quantity and quality of soil nutrients [19, 20]. This negative impact of exotics grazers on plants can consequently affect native insects and how these effects spread along the trophic chain by indirect interactions, impacting ecosystem attributes and functioning [21].

Impact by Humans

This was known already 50 years ago. Fibre farming (i.e., the total utilization of tree crops grown on short rotations) raises the spectre of soil impoverishment of nutrients requiring nutrient management and careful evaluation of future tree productivity of the loss of nutrients [22].

Ultimately, there is no doubt that cropping must be viewed as a medium to long-term option (> 7 years) for impoverishing the arable soils [23]. Intensively used agricultural production soils are vastly micronutrient deficient [24]. Soil impoverishment (although limited to nitrogen balance) thus can only be achieved when removal of nutrients (removal of cuttings and hay) exceeds atmospheric input [25]. But, greater . Nutrient depletion associated with biomass harvesting potentially leads to ecosystem impoverishment, as nutrient amounts depend not only on nutrient concentrations of biomass, but also on biomass production, harvest frequency and intensity of biomass removal [26].

N, unlike P, Ca, K and other micro and macronutrients, is absent in bedrock, glacial tills and the other unweathered precursors of soil, but is abundant in the atmosphere as N2 gas, although N fixers are needed to avoid N-limitation of the soil [27].

Soil acidification

One of the major causes of soil impoverishment and soil acidification is a decoupling of the ion cycle in the ecosystem due to the loss of watering of the soil with flooding derived from atmospheric rock weathering . This is a direct result of the fact that rocks contain only bases and no acid precursors so soils cannot acidify if water comes from rocks (mountains) [28]. The ecosystem ion cycle is the following:

1. A consumption of protons in rocks and soils results in a decrease of their acid neutralizing capacity (ANC) and can result in the buildup of a base neutralizing capacity (BNC). Strong soil acidification leads to the formation of stronger acids from weaker acids in the solid phase; this may be connected with a decrease in the BNC.
2. Weak acids (carbonic acid) lead in geological times to the depletion of bases without a larger accumulation of labile cation acids. Strong acids (HNO_3, organic acids, H_2SO_4) can lead within a few decades to soil acidification, i.e. to leaching of nutrient cations and the accumulation of labile cation acids.
3. The acid input caused by the natural emission of SO_2 and NO_x can be buffered by silicate weathering even in soils low in silicates.
4. The cause of soil impoverishment and soil acidification is a decoupling of the ion cycle in the ecosystem.
5. Acid deposition in forest ecosystems which persists over decades leads to soil acidification.

6. Formation and deposition of strong acids with conservative anions (SO_4, NO_3) shifts soil chemistry into the Al or Al/Fe buffer range up to great soil depth. In such soils eluvial conditions prevail throughout the solum and even in upper part of the C horizon: in connection with the decomposition of clay minerals, Al and eventually Fe are being eluviated. The present soil classification does not include this soil forming process.
7. In the long run, soil acidification by acid deposition results in the retraction of the root system of acid tolerant tree species from the mineral soil, and in water acidification.

This factual loss of nutrients could have been a process that has taking place for several hundreds of years.

Consequences

The factual loss of nutrients is further confirmed by its aftereffects.

As a primary consequence of soil impoverishment is soil erosion and land impoverishment, which is due to the loss of fertile topsoil with its load of organic matter and nutrients [29]. By reducing the amount of organic matter and nutrients the whole soil ecosystem is thrown into disarray with direct negative influences on bacteria and fungi.

A second indirect consequence which is obvious from the quantities of micronutrients in soil is the amount of micronutrients absorbed by the plant. The higher the levels of essential nutrients for plants (especially iron [Fe], zinc [Zn], manganese [Mn], copper [Cu], nickel [Ni], Boron [B], molybdenum [Mo] and chlorine [Cl]), the higher the levels in the plant [30].

One of the major consequences of poor mineral content in soil (and subsequently low concentrations of suitable metabolites) is poor fungal growth and fungistasis [31]. Fungi are fundamental in the delicate equilibrium of plants as they provide together with bacteria the necessary micronutrients to the vegetable kingdom. An example is the capacity of plants and associated microbes to adopt interacting strategies to obtain iron from the soil: microorganisms can transform insoluble metallic oxides into metallic chelates (siderophores as iron chelates) useful to plants [32]. Metal chelates provided by bacteria and fungi are then considered to be important ecological determinants and factors in the nutrition of plants.

The structures and functions of the plant will necessarily change to adapt to the new nutritional situation of the soil. Another example shows that the root physiological and morphological properties of a plant change along a gradient of soil phosphorus availability in the tropical montane forests [33]. This confirms how variable are plants and what type of physiological changes could occur when there is lower micronutrient availability.

Soil impoverishment can also cause changes in the composition of invertebrate communities (especially arthropods) dwelling in or on top of the soil [34]. Their ecology also has influences on the plants of that ecosystem.

Ultimately, micronutrient deficient soils do not only have an impact on crop production, but also have negative effects on human nutrition and health [24]. This aspect of moving a micronutrient from the soil to the microbial, vegetal and then animal (livestock and humans) kingdom has amply been studied over the past few decades and minimum soil micronutrient levels in relation to animal requirement have long been reviewed [35]. The study of micronutrients in soil/plant/animal interfaces has revealed two types of deficiencies: clinical and subclinical. While clinical signs are those that are obvious to see and a diagnosis is relatively simple and straightforward, a subclinical sign is more problematic [36]. The latter (subclinical) are also the more common in the animal population lasting longer and affecting livestock production (by impacting their health) and can be solved only by active micronutrient supplementation.

It has been known at least since the 1960s that certain micronutrients which are present in sufficient amounts for the plant requirements are totally inadequate to sustain animal life [37]. Even earlier, it was shown that adding minimum amounts of certain micronutrients or trace elements (Cobalt [Co], Fe, Cu, Zn and Mn) can correct micronutrient deficiency in vegetation and malady in livestock of to increasing the amounts needed for humans [38]. In most sheep, cattle, and deer who graze pasture year-round, inadequate intake of cobalt, copper, iodine and selenium is prevalent. In these animals, suitable supplementation methods suited to grazing livestock (long-lasting injections, etc.) have been developed [39]. These supplementation methods (vitamin–mineral pre-mixes) are effective in improving micronutrient nutrition, and, consequently, the reproductive performance and overall productivity of farm animals [40].

Supplementation

To avoid the resurgence of micronutrient deficiencies or the hidden hunger, several strategies have been adopted [41]. Among these biofortification of foods and the use of supplements are the most common.

Biofortification of food can be done with plant breeding techniques, by genetically modifying the plants [42], or by improving agronomical efficiency. The basis of this change is that different cultivars may absorb various levels of micronutrients in the same soil type (improvement of root system) and the absorption pattern may be different (some plants species may be able to extract more of a nutrient than other in the same conditions) [43].

Since supplementation has been shown to be absolutely effective on animals, it seems the most logical solution also for humans (refer to the previous section). For humans, as for animals the most challenging situation is that of an unforeseeable subclinical deficiency. Being mammals, both humans and livestock (cattle, etc.) suffer from the same forms of deficiencies (clinical and subclinical manifestations of diseases) to roughly the same micronutrients [36]. Moreover, these micronutrients have to be in a highly bioavailable form to be absorbed and maximally utilized by each individual. This has been shown extensively in observational studies on children development [44].

Quantitative

The only remaining point to define concerning micronutrient supplementation is their quantities. As already described in the introduction, both the EU and the FDA have set the normal ranges for the major micronutrients (vitamins or minerals). But, all nutrients should be given in an effective range, i.e., a range in which the body can maximally utilize the micronutrient at full capacity. In order to avoid subclinical deficiencies, it is advisable that, the dose of the nutrients should be increased to remain below the maximum dose as defined by all recognized international guidelines (ULs).

It should also be noted that increased amounts of micronutrient may answer to a different pharmacokinetic (PK) rule. It is known that total amount of micronutrients that are absorbed increase with intake, although this percentage absorption decreases with increasing doses, suggesting that there is a saturation process ongoing of the absorption mechanisms [45]. Other micronutrients at higher intakes (pharmacologic doses) bypass this carrier dependent transport system and are absorbed by simple diffusion (EFSA, 2006).

A list of current ULs for vitamins and minerals from both the EU and US HA is presented in Table 1.

Table 1: UL and RDVs from EU and US sources (per day)

Micronutrient	EFSA 2019 (UL)	DRI 2019 (UL)	DRV 2019	RDA
Vitamin A	20 mg (n/d)	3000 µg	700 µg	770 µg
Vit. B1 (Thiamine)	n/d	n/d	0.9 mg	1.4 mg
Vit. B2 (Riboflavin)	n/d	n/d	1.4 mg	1.4 mg
Vit. B3 (Niacin or Nicotinic acid)	n/d	35 mg	13 mg	18 mg
Vit. B5 (Pantothenic Acid)	n/d	n/d	n/a	6 mg
Vit. B6 (Pyridoxine)	25 mg	100 mg	1.2 mg	1.9 mg
Vit. B7 (Biotin)	n/d	n/d	n/a	30 µg
Vit. B9 (Folic Acid)	1000 µg	1000 µg	300 µg	600 µg
Vit. B12 (Cobalamin)	n/d	n/d	1.5 µg	2.6 µg
Vit. C (ascorbic acid)	n/d	2000 mg	50 mg	85 mg
Vit. D	100 µg	100 µg	20 µg	15 µg
Vit. E	300 mg	2000 mg	n/a	15 mg
Vit. K	n/d	n/d	n/a	90 µg
Iron	n/d	45 mg	14.8 mg	27 mg
Zinc	25 mg	40 mg	7.0 mg	11 mg
Iodine	600 µg	1100 µg	140 µg	220 µg
Magnesium (Mg)	250 mg *	350 mg	270 mg	350 mg
Manganese	n/d	11 mg	n/d	2.0 mg
Copper	n/d	10000 µg	1.2 mg	1000 µg
Calcium	2500 mg	2500 mg	700 mg	1000 mg
Phosphorus	n/d	3.5 g/d	550 mg	700 mg
Chromium	n/d	n/d	n/a	30 µg
Boron	10 mg	20 mg	n/a	n/a
Fluoride	7 mg	10 mg	n/a	3 mg
Chloride	n/d	3.6 g	2500 mg	2.3 g
Molybdenum	0.6 mg	2000 µg	n/a	50 µg
Nickel	n/d	1.0 mg	n/a	n/a
Potassium	n/d	n/d	3500 mg	4.7 g
Selenium	300 µg	400 µg	60 µg	60 µg
Sodium	n/d	n/d	1600 mg	1.5 g/d
Vanadium	25 mg	n/d	n/a	n/a

n/d=not defined. UL for EFSA 2019 (https://www.efsa.europa.eu/sites/default/files/assets/UL_Summary_tables.pdf)

Those vitamins and minerals highlighted in green represent the micronutrients which do not have a defined UL. Therefore, there is no risk in increasing the dosages per day well beyond the limits recommended by the international HA.

In general, vitamin Bs without a declared UL are known to have been given to healthy and unhealthy individuals at doses of at least 40 times the RDA without any adverse reaction.

Some such examples include vitamins B1, B2 and B3. Vitamin B1 (thiamine) is known to be useful in several pathological conditions and has been given at doses of 20 to 30 mg per day (d) for several weeks without any adverse events [46]. In a study from certain areas of the world, thiamine supplementation of 100 mg/d was found to be sufficient to counteract the lowering of thiamine status resulting from the consumption of vitamin B1 sequestering foods [47]. Similarly, riboflavin (vitamin B2) was administered at much higher doses than standard RDA values (up to 90 mg for 5-8 weeks) to parkinsonian patients [48]. No AE was noted (only some beneficial effects), confirming again that UL could not be established The same results occur with niacin (vitamin B3), which has been used extensively in clinical trials at 25-50 mg/kg [49].

Other water-soluble vitamins have also been experimentally given at high doses without adverse effects, including vitamin B5 (pantothenate) at 10 g/d, vitamin C (ascorbic acid) at 3-5 g/d (with only mild bloating and diarrhea) and folate (vitamin B9) at 600 g/d [50].

These experimental results suggest that micronutrients can be assimilated at much higher doses than normally advocated by HAs (up to 40-50 times), without risking AEs.

Vitamins & Minerals

Finally, without prejudice of other extremely well-presented and comprehensive reviews of micronutrient already completed in the past, a few considerations for each major micronutrient will be proposed hereafter. The scope is to show their importance and how the amounts are necessary for maximal health maintenance of the cells and tissues of the human body as a whole.

Vitamin A

Vitamin A (β-carotene or retinol) belongs to the category of substances known as antioxidants, utilized by the body to protect itself from a variety of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Such molecules reduce the oxidative stress of a cell. Oxidative stress is defined as the exposure to oxidants (ROS and RNS) generated endogenously or exogenously from a variety of sources. Vitamin A is an important for a variety of physiologic functions including normal vision, gene expression, reproduction, embryonic development, growth, and immune function [51, 52].

Vitamin B1

Thiamine (B1) is a water-soluble vitamin with many functions that include acting as a fundamental coenzyme in the metabolism of carbohydrates and branched-chain amino acids. Vitamin B1 is therefore essential in energy metabolism and is used extensively by lipid (fat) and nucleotide synthesis enzymes. Thiamine is required as a coenzyme in all tissues and is found in high concentrations in skeletal muscle, heart, liver, kidneys and brain [53-56].

Vitamin B2

Riboflavin, another water soluble and heat stable vitamin, is necessary for normal development, lactation, physical performance, and reproduction. It is used by the body to metabolize fats, protein, and carbohydrates into glucose for energy in the form of two coenzymes, flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). This vitamin is not present in sufficient quantities in vegan diets and should be supplemented regularly [57-59].

Vitamin B3

Niacin, probably the most important water-soluble B complex vitamin, is linked to energy pathways and DNA repair and replication. Niacin is the precursor of several active coenzymes such as NAD (nicotinamide adenine dinucleotide) and NADP (nicotinamide adenine dinucleotide phosphate) and is involved in energy-requiring and energy-generating cellular reactions, and in the regulation of the lipid status, i.e., cholesterol, apolipoprotein B, triglycerides, and lipoproteins [54, 60].

Vitamin B5

Pantothenic acid (vitamin B5) is a component of coenzyme A (CoA), involved in fatty acid metabolisms (such as ketone bodies synthesis from beta-oxidation of fatty acids). This essential to life vitamin is a fundamental cofactor in a wide variety of metabolic processes, including transfer (acyl carrier protein) in fatty acid and carbohydrate metabolism (in the Krebs cycle). Pantothenic acid deficiency can create various symptoms among which sleep disturbance, fatigue and apathy, are the most well-known [54, 61, 62].

Vitamin B6

Vitamin B6 (also known as pyridoxine, pyridoxal, and pyridoxamine) is yet another water-soluble vitamin, important as co-enzyme in protein metabolism and in the development of the central nervous system (CNS) [63]. It is uniqueness is linked to the fact that it has so many functions as it is required for the activity of around 100 enzymes with key roles in several metabolic processes. In the context of the CNS, vitamin B6 has a vital role in the synthesis of neurotransmitters (such as dopamine, norepinephrine, *γ*-aminobutyric acid [GABA] and histamine). Moreover, vitamin B6 is also known to be fundamental in the conversion of tryptophan to niacin (vitamin B3), one of the major cross-interaction of micronutrients at the level of physiologic processes [54, 64].

Vitamin B7

Biotin, an essential water-soluble B-vitamin (or cofactor) with many key roles in human metabolism, is a heterocyclic compound, that cannot be synthesised by mammals. Biotin has many functions as a cofactor for enzymes involved in fatty acid synthesis and oxidation and for mitochondrial metabolism. Biotin exists as free biotin and in protein-bound forms in foods, and at high intakes, it is absorbed by simple diffusion. Although biotin is widely distributed in natural food, its concentration varies substantially. For example, liver contains biotin at about 100 μg/100 g whereas fruits and most meats contain only about 1 μg/100 g. Biotin intake provides full potential achievement [54, 61, 65, 66].

Vitamin B12

Vitamin B12, a water-soluble vitamin also known as cobalamin, can be present in several forms forms including cyano-, methyl-, deoxyadenosyl- and hydroxy-cobalamin and is crucial for DNA synthesis and for cellular energy production. Vitamin B12 is the coenzyme for only two reactions in the body: the interconversion of two substrates in the fatty acid breakdown process and the conversion of homocysteine to methionine (working in concert with folate for the synthesis precursors of DNA and RNA). Vitamin B12 deficiency is common, and is associated with gastrointestinal complaints related, sometimes, to the underlying gastric disorder in pernicious anaemia [45, 54, 67].

Vitamin C

The data on vitamin C (ascorbic acid) is vast and myriads of studies have been completed on this essential vitamin since its first use by dr. Klenner in the 1940s. Of note is the fact that at higher than normal quantities is remarkably nontoxic at high levels (10 to 100 times the recommended dietary allowance when taken orally), vitamin C is remarkably nontoxic [68, 69]. There is no evidence suggesting that vitamin C is carcinogenic or teratogenic or that it causes adverse reproductive effects. Even HA reviews of high vitamin C intakes have indicated low toxicity and no AEs have been reported after very large doses (greater than 3 g/day) [52].

Vitamin C is not only an antioxidant but also a powerful antimicrobial against countless species including uropathogenic strains of E. coli and K. pneumoniae [70], agents causing respiratory infection [71], common cold and hepatitis [72], depending on the doses given [73]. Larger quantities of vitamin C have been shown to be an effective and potent immune system stimulator when high glycemic dietary carbohydrates are restricted, since its absorption is inhibited by the presence of glucose through competition for the same multimembrane-spanning facilitative transporter Glut1 [74]. Therefore, vitamin C should be taken at low carbohydrate diets to facilitate its absorption, failing which would consequently render the consumption of vitamin C futile. The role for vitamin C in the immune response is huge (neutrophil functions, including chemotactic responses, phagocytosis, hexose monophosphate and monocyte-macrophage reactivity) as is in some hormonal components of the nervous system the likes of which is simply unrivalled [52, 75].

Vitamin D

Vitamin D (calciferol) is unique in that it is a substance photosynthesized in the skin of vertebrates by the action of solar ultraviolet B radiation. Vitamin D has a major biologic function in humans to maintain serum calcium and phosphorus concentrations within the normal range. Although sunlight triggers the formation of Vitamin D in human skin, studies proved that, despite high exposure to the summer months, high prevalence of Vitamin D deficiency can be found. Vitamin D deficiency is characterized by inadequate mineralization or demineralization of the skeleton and studies confirm Vitamin D supplementation is much better than Calcium instead [76-78].

Iodine

Iodine is an essential dietary element for mammals since it is required for the synthesis of the thyroid hormones thyroxine (T4, 3,5,3’,5’-tetraiodothyronine), containing 65% by weight of iodine, and its active form T3 (3,5,3’-triiodothyronine), containing 59% by weight of iodine. Iodine is present naturally in iodized salt, seaweeds, fish and seawater [79]. A single annual dose of 400 mg of iodine supplements or a daily dose of 150 µg are recommended by the WHO to avoid deficiency [80, 81]. By back-calculating the amount being used by the WHO, the resulting daily dose is 1 mg. Sufficient iodine intake is necessary to support health by forming thyroid hormones. Failure to achieve this will cause iodine deficiency (goitre, neurocognitive impairments, and in severe cases, hypothyroidism ultimately resulting in cretinism), linked to reduced production of thyroid hormones [61, 82, 83].

Although the DRV and RDA stipulate that 220 µg is the recommended daily dose, the amount of iodine the Japanese consume daily from seaweeds has been estimated to be within the safe upper limit of 3 mg/day (based a conservative computation). Data was obtained by estimating the daily urinary excretion of iodine. Iodine-induced hyperthyroidism (IIH) has been reported as a side effect of iodine supplementation. This is also called as "Jod-Basedow phenomenon" has been observed in people consuming high amounts of iodine (28 mg–140 mg of iodine per day) [84-86]. Finally, iodine have well-known antiseptic properties: it is an antimicrobial and effective fungicidal, viricidal and sporicidal agent. Iodine has also been used in water treatment (disinfection) since 1900s, in the quantities of 2.5 to 7.0 mg/L, the long term ingestion of which failed to elicit any harmful effects [79, 87, 88]. These properties combined together make iodine one of the most critical elements that can restore the equilibrium of the resident microflora of the human holobiont at the safe daily amounts between 1 and 14 mg per day.

Selenium

As an example of a metal or cation (positive ion), selenium was chosen for its special use in DNA damage and repair. Selenium is a micronutrient known to improve antioxidant defences involved in the prevention of DNA damage or enhancement of DNA repair [89]. Selenium deficiency seldom causes unconcealed illness when it occurs in isolation. Nevertheless, it leads to biochemical changes that predispose to disease associated with other stresses and stressors (factors inducing stress on the system) [52].

Overall, the functions of these micronutrients suggest that there is a need consume them in the right amounts not just to reduce the clinical signs of deficiencies but also the subclinical manifestations. Special attention should also be given to vitamin C and iodine as regulators of immune response and equilibrators for the holobiont.

Conclusions

Micronutrient type and quantity have been reviewed with a light on their effects on the holobiont as a system of resident bacteria and eukaryotic cells. Essential micronutrients have a multivariate and polyhedral role in the maintenance of an equilibrium (health) within the disparate microbial communities that populate the numerous ecosystems that compose the human body.

Given the following considerations

1. The amount of micronutrients that are consumed every day
2. The importance of micronutrients for each physiologic process that occur in the cells and outside of the ECM
3. Loss of micronutrients in the soil which was already clear from livestock deficiencies in 1960s
4. The success of supplementation at high quantities to livestock
5. The presence of subclinical deficiencies

It becomes vital that micronutrients are consumed at amounts that stand around 40 times those recommended as DRV or RDA. As animals first and holobiont second, we humans have to look at nature and follow its rules. If livestock thrive with supplementation, it is not an unfair statement that we too should benefit from daily micronutrient supplementation to maintain the health granted by our internal microbial communities (equilibrium) [6, 90].

By pulling together the factors that make up nutrition as a whole (by merging together the knowledge handed down by ancient medicine and acquired through decades of research) we could truly strive to get closer to a holistic nutrition, one that is befit to the holobiont [91].

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